UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

DATE: August 30, 2016

SUBJECT: **2-Phenylphenol:** Summary of Hazard and Science Policy Council (HASPOC) Meeting on July 21, 2016: Recommendations on the Requirements for Immunotoxicity Study (OCSPP 870.7800).

PC Codes: 064103, 064104, 064108
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: N/A
TXR No.: 0057473
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A
CAS Nos.: 90-43-7, 132-27-4, 13707-65-8
40 CFR: N/A

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MEETING ATTENDEES

HASPOC Members: Anwar Dunbar, Anna Lowit, Elizabeth Mendez, Jeff Dawson, Jonathan Leshin, Kelly Lowe, P.V. Shah, Ray Kent, Uma Habiba, Vincent Chen

Presenter: Tim McMahon

Other Attendees: Thurston Morton, Tim Dole, Rachel Ricciardi, Sarah Dobreniecki

I. PURPOSE OF MEETING

The Risk Assessment and Science Support Branch (RASSB) of the Antimicrobials Division (AD) is conducting reregistration review for 2-phenylphenol. In accordance with 40 CFR 158W (Toxicology Data Requirements for Antimicrobial Pesticides), an immunotoxicity study (OCSPP 870.7800) is considered as a data gap not in the 2-phenylphenol toxicity database. The Hazard and Science Policy Council (HASPOC) met on July 21, 2016, to evaluate the need for this study.

II. SUMMARY OF USE PROFILE & PREVIOUS RISK ASSESSMENT

a. Use Profile

2-phenylphenol is a pesticide with both agricultural and antimicrobial uses. 2-phenylphenol is used as an antimicrobial pesticide for applications to hard surfaces, (walls, floors, barns) agricultural premises and equipment, air deodorization, commercial and institutional premises, medical premises, residential and public access premises (carpet, hard surfaces, crack and crevice treatment), and material preservatives (stains, and paints, metal working fluids, textiles, paper slurries and cement mixtures, glues, and adhesives, and consumer, household and institutional cleaning products).

As an agricultural pesticide, 2-phenylphenol is used as a post-harvest fungicide with several tolerances listed in 40 CFR 180.129, including lemon, lime, orange, tangerine, tomato, bell pepper, cucumber, pineapple, grapefruit, kumquat, cantaloupe pulp and citron citrus fruit crops. A 20ppm tolerance exists for plums, prunes, carrots, peaches and kiwi fruit. There is also a 25ppm tolerance for apples and pears in addition to a 125ppm tolerance for whole cantaloupe. Dietary exposure to 2-phenylphenol can occur from use as a disinfectant or sanitizer on hard food-contact surfaces in food processing plants, on conveyor belts in food processing plants, on hard surfaces and equipment in farm premises, hatcheries, and animal/poultry housing facilities, on hatching eggs, in adhesives, mineral slurries, pigments and fillers for food-contact paper, in process water systems of paper mills as a slimicide, and in process water systems of sugar beet mills. Drinking water exposure is not expected from 2-phenylphenol.

Residential handler exposure is expected from uses of 2-phenylphenol, including use on indoor and outdoor hard surfaces, air deodorization, fogging, treated plastics, and treated paint (dermal and inhalation). Residential post-application exposure to 2-phenylphenol is expected from contacting treated hard surfaces/floors (dermal and incidental oral exposure to children), wearing treated clothing (dermal exposure to adults and children), wearing treated diapers (dermal exposure to infants), mouthing treated textiles such as clothing and blankets (incidental oral exposure to children), and mouthing treated plastic toys (incidental oral exposure to infants). Additionally, postapplication/bystander inhalation exposures were assessed for use of the disinfecting/deodorizing products (vapor exposure to adults and children) and paints (vapor exposure to adults and children).

Occupational handler exposures to 2-phenylphenol may occur in numerous scenarios under the Use Site Categories (USC) of agricultural premises, food handling premises, commercial/institutional/industrial premises, and medical premises. Additionally, occupational exposure can occur during the preservation of materials that are used for household, institutional, and industrial uses, along with the preservation of wood.

b. Toxicity Profile

2-phenylphenol is moderately toxic via the oral route (category III) and weakly toxic by the dermal route (category IV). 2-phenylphenol is a severe dermal irritant but is not a dermal sensitizer. There is insufficient information to assess acute inhalation toxicity or eye irritation potential.

Metabolism data for 2-phenylphenol show a dose-dependent metabolic profile. At doses below approximately 200 mg/kg, ortho-phenylphenol is found primarily in urine as the glucuronide and sulfate conjugates in both rats and mice. At higher doses, formation of phenolic metabolites (such as 2,4'-dihydroxyphenyl and phenylhydroquinone) in the liver through the action of cytochrome P-450 by rat CYP2C11 and possibly CYP2E1, and human CYP1A2 can predominate. Further conversion of phenolic metabolites is postulated to be related to the carcinogenic mode of action for 2-phenylphenol.

In a subchronic oral toxicity study in rats, dietary exposure to 2-phenylphenol resulted in mortality at doses in excess of 2000 mg/kg, and decreases in hemoglobin and hemoglobin concentration at doses in excess of 1000 mg/kg. Inflammation of the kidneys in both male and female rats and abnormal growth in the mucous membrane of the male bladder was also observed. The bladder is a target organ of 2-phenylphenol.

A 21-day dermal toxicity study produced no systemic toxicity up to and including a dose of 1000 mg/kg. Dermal irritation was observed at 500 and 1000 mg/kg/day.

The database for developmental toxicity is considered complete with an acceptable study in the rat and rabbit. In the rat, minimal maternal toxicity was evident, and there was no evidence of developmental toxicity. In the rabbit, treatment-related alterations in microscopic kidney structure, primarily consisting of inflammation and tubular degeneration, were noted in high-dose animals. Observations of blood in the feces, urine, or cage pan was also noted. There was no evidence of developmental toxicity.

In a 2-generation reproduction toxicity study, decreases in weight gain and food consumption were observed in male and female parental animals. Urinary bladder calculi, transitional cell hyperplasia, and chronic inflammation of the urinary bladder were observed in male parental animals. No treatment-related effects on reproductive function or performance were observed in male or female rats of either generation

An analysis of the genetic toxicology data from over 130 studies with 2-phenylphenol was undertaken by Brusick (2005) who found that there was no indication of gene mutations in bacteria or in mammalian cells such as Chinese hamster ovary (CHO) cells and that positive results with mouse lymphoma ($Tk^{+/-}$) were generally associated with cytotoxicity. Similarly, clastogenicity, which was the most frequently observed type of genotoxicity, was consistently linked with cytotoxicity.

Carcinogenicity studies with 2-phenylphenol were conducted in rats and mice. In rats, males had significant increasing trends, and significant differences in the pair-wise comparisons for urinary bladder papillomas, transitional cell carcinomas, and papillomas and/or transitional cell carcinomas combined, all at $p < 0.01$. There were no compound-related increases in tumors in female rats. In mice, males had significant increasing trends, and significant differences in the pair-wise comparisons for liver adenomas and adenomas and/or carcinomas combined, all at $p<0.01$. Female mice had a significant difference in the pair-wise comparison for liver carcinomas at $p< 0.05$.

In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), the CARC classified 2-phenylphenol as "Not Likely to be Carcinogenic to Humans" based on convincing evidence that a non-linear mode of action for bladder tumors was established in rats.

c. Previous Risk Assessment

2-phenylphenol was previously assessed in the Reregistration Eligibility Decision Document (RED) that was published in July of 2006. In the RED, a dietary risk assessment (food only) was performed, as well as dermal and inhalation exposures from occupational and residential uses of products containing 2-phenylphenol. An acute dietary aggregate risk assessment was not conducted as there was no endpoint of concern. A chronic dietary aggregate assessment was conducted and showed no dietary risks of concern for 2-phenylphenol. Short- and intermediate-term aggregate risk was assessed for adults and children that could be exposed to 2-phenylphenol and 2-phenylphenol salt residues from the use of products in nonoccupational environments. Short- and intermediate-term aggregate risks were not of concern, with the exception of dermal post-application exposures to adults and children from treated textiles.

An acute dietary endpoint for 2-phenylphenol for the general population and females 13-49 was not identified in the database.

For chronic dietary risk assessment, the NOAEL of 39 mg/kg/day was selected from a combined chronic toxicity/carcinogenicity study in rats, based on decreased body weight, body weight gain, food consumption and food efficiency, increased clinical and gross pathological signs of toxicity.

For short-term (1-30 days) incidental oral risk assessment, the NOAEL value of 100 mg/kg/day was selected from the developmental toxicity studies in rats and rabbits, based on clinical observations of toxicity, decreased weight gain, food consumption and food efficiency observed in the rat developmental toxicity study.

For intermediate-term (30 days-6 months) incidental oral risk assessments, the NOAEL of of 39 mg/kg/day was selected from a combined chronic toxicity/carcinogenicity study in rats, based on decreased body weight, body weight gain, food consumption and food efficiency, increased clinical and gross pathological signs of toxicity.

For short-term dermal risk assessment (1-30 days), a NOAEL of 100 mg/kg/day was selected from the 21-day dermal toxicity study in rats, based on dermal irritation (erythema, scaling) at the site of test substance application at the next highest dose of 500 mg/kg/day. This is a route-specific study and is also appropriate for the time frame of the risk assessment.

For intermediate-term and long-term dermal risk assessments, the NOAEL of of 39 mg/kg/day was selected from a combined chronic toxicity/carcinogenicity study in rats, based on decreased body weight, body weight gain, food consumption and food efficiency, increased clinical and gross pathological signs of toxicity. A dermal absorption factor of 43% was used based on submitted data.

For short-term inhalation risk assessments (1-30 days), the NOAEL of 100 mg/kg/day was selected from the developmental toxicity studies in rats and rabbits, based on clinical observations of toxicity, decreased weight gain, food consumption and food efficiency observed in the rat developmental toxicity study.

For intermediate-term and long-term inhalation risk assessments, the NOAEL of 39 mg/kg/day was selected from the combined chronic toxicity/carcinogenicity study in rats, based on decreased body weight, body weight gain, food consumption and food efficiency, increased clinical and gross pathological signs of toxicity.

III. STUDY WAIVER REQUESTS

A. Immunotoxicity Study

To determine the need for data to address immunotoxicity, the Office of Pesticide Programs (OPP) uses a weight of evidence approach that includes (1) examination of the overall toxicity profile of the chemical and evidence of immunotoxicity, and (2) evidence of immunotoxicity in the database for structurally related chemicals and/or those with the same MOA. Examination of the toxicity profile for potential indicators of immunotoxicity includes hematology indicators (particularly elevated or depressed white blood cell counts or white cell differential), clinical chemistry indicators (particularly a shift in albumin/globulin ratio), changes in absolute or relative spleen and thymus weight in conjunction with histopathological alterations, and histopathology of lymphoid tissues.

1. **Indicators of potential immunotoxicity**The effects observed in the toxicity database for 2-phenylphenol with respect to potential immunotoxicity are summarized below.

Parameter	Findings
Hematology Indicators (WBC changes)	There were no changes in hematology measurements indicative of immunotoxicity for 2-phenylphenol.
Clinical Chemistry Indicators (A/G Ratio)	There was no evidence of clinical chemistry changes indicative of immunotoxicity for 2-phenylphenol.
Organ Weight Indicators (Spleen, Thymus)	Decrease in relative thymus weight (non-significant) observed in BALB/C mice administered 2-phenylphenol for 28 days at 15 mg/kg (Nakata et al., 2013). Decreased absolute spleen weights in mice at 250 mg/kg/day in a mouse carcinogenicity study.

Histopathology Indicators (Spleen, Thymus, Lymph nodes)	There were no histopathology indicators from the available toxicity studies on 2-phenylphenol.
Toxicity Profile (Target Organs)	The kidney, urinary bladder and skin are targets of 2-phenylphenol toxicity.

2. **Evidence for Immunotoxicity in the Database of Other Similar Chemicals:** A 28-day drinking water study with phenol conducted by the National Toxicology Program but not peer reviewed showed no evidence of immunotoxicity. Decreased antibody production in response to immunization with SRBC was observed in one study with phenol (Hsieh et al., 1992) but was not replicated by others. Immunotoxicity from oral exposure to pentachlorophenol has been observed. In mice, delayed splenic antibody production and serum antibody titers was observed as well as decreases in the magnitude of the IgG and IgM responses and decreased complement pathway activity. However, some or all of these effects may be due to the dioxin and furan contaminants of pentachlorophenol.

Based on a WOE approach, considering all the available information for 2-phenylphenol hazard and exposure data, the HASPOC recommends that an immunotoxicity study is not required at this time. This approach included all of the following considerations: (1) there were no hematological indicators of immunotoxicity in the 2-phenylphenol toxicity database; (2)decreased relative thymus weight in mice administered 2-phenylphenol for 28 days at 15 mg/kg was not significantly different from control and decreased spleen weight in mice was observed at a dose (250 mg/kg) above the current regulatory endpoints; (3) there are no histopathological indicators of immune system toxicity; (4) the immune system is not a target organ of 2-phenlphenol toxicity; and (5) The structurally related chemical phenol shows no evidence of immunotoxicity; immunotoxicity of pentachlorophenol is likely due to dioxin and furan contaminants.

IV. HASPOC Conclusions

The HASPOC, based on a WOE approach, considering all of the available hazard and risk information for 2-phenylphenol, recommends that the immunotoxicity study **is not required** for 2-phenylphenol at this time.